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Tuberculosis and OPAT

Helena A White
Infectious diseases consultant
Leicester

One team shared values

Outline

- Why OPAT may be needed for TB management
- Injectable agents
- Monitoring/toxicity
- Directly Observed Therapy (DOT) considerations

Injectable agents generally not needed for fully sensitive or mono-resistant strains of TB

Standard treatment 6 months
9 months for B+J infections
12 months for CNS infections

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Notice to Readers

Revised Definition of Extensively Drug-Resistant Tuberculosis

In a report published on March 24, 2006, *MMWR* reported that CDC, in collaboration with the World Health Organization (WHO) and participating supranational reference laboratories, had agreed to define extensively drug-resistant tuberculosis (XDR TB) as cases of TB disease in persons whose *Mycobacterium tuberculosis* isolates were resistant to isoniazid and rifampin and at least three of the six main classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicyclic acid) (*1*). Since that original publication, additional reports have documented the presence of XDR TB in Iran and South Africa with high mortality among persons infected with human immunodeficiency virus (HIV) who are benefiting from antiretroviral therapy (*2,3*).

The emergence and transmission of these strains of *M. tuberculosis* highlight the urgency of strengthening national TB and HIV/acquired immunodeficiency syndrome control programs worldwide, particularly in settings with high HIV

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Extensively drug-resistant tuberculosis in the UK: 1995 to 2007

I Abubakar,[1] J Moore,[1] F Drobniewski,[1] M Kruijshaar,[1] T Brown,[1] M Yates,[1] C Anderson,[1] E G Smith,[2] J Magee,[3] M Lipman,[4] J McMenamin,[5] M Ruddy,[6] J M Watson[1]

ABSTRACT

Background: The emergence of multidrug-resistant tuberculosis (MDRTB) and extensively drug-resistant tuberculosis (XDRTB) is a threat to global tuberculosis control. Limited information is, however, available on the outcome of XDRTB cases. This study describes the susceptibility to second- and third-line antituberculosis drugs among MDRTB cases and treatment outcome of identified XDRTB cases.

Method: The results of second-line antituberculosis drug susceptibility tests in the UK between January 1995 and December 2007 were retrospectively reviewed and clinicians contacted for treatment outcome of XDRTB cases. Participants included all 678 patients with culture-confirmed MDRTB in the UK. The main outcome measures were the proportion of isolates resistant to second-line antituberculosis drugs and treatment outcome for XDRTB cases.

Results: Among MDRTB isolates, levels of resistance to amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide and *p*-aminosalicylic acid (PAS) were 5.5, 3.4, 5.6, 5.1, 14.0 and 16.7%, respectively. Six XDRTB cases (0.9% of MDR cases) were identified during this period. Two further cases of XDRTB were reported in 2008. Five individuals with XDRTB died of tuberculosis within 3 years

the incidence of MDRTB has risen, although the magnitude of the increase is small.[6] Here we describe the susceptibility to second- and third-line antituberculosis drugs among MDRTB cases in the UK between January 1995 and December 2007 and report the number, characteristics and treatment outcome of identified XDRTB cases.

METHODS

Study population

The results of drug susceptibility testing of all *M tuberculosis* complex isolates undertaken between 1995 and 2007 have been collated through the UK Mycobacterial Surveillance Network (MycobNet) collaboration. Results of drug susceptibility to the six main classes of drugs used to treat MDRTB (fluoroquinolones, serine analogues, aminoglycosides, capreomycin, *p*-aminosalicylic acid (PAS) and the thionamides) and other agents (clarithromycin, azithromycin, rifabutin, streptomycin and clofazimine) were analysed. Duplicate results from isolates were manually removed by using patient names, date of birth and address where available. It is, however, possible that a small number of duplicate records remain due to the limited

Definitions

- MDR-TB – Rifampicin and Isoniazid resistant

- XDR-TB – Rifampicin and Isoniazid resistant
  - Plus resistance to one injectable agent (Capreomycin/Amikacin/Kanamycin)
  - Plus resistance to any fluoroquinolone

MDR/XDR-TB

- More difficult to treat (more drugs/toxicity)
- Longer treatment courses

- Not more infectious….but…..public health implications if disease spreads

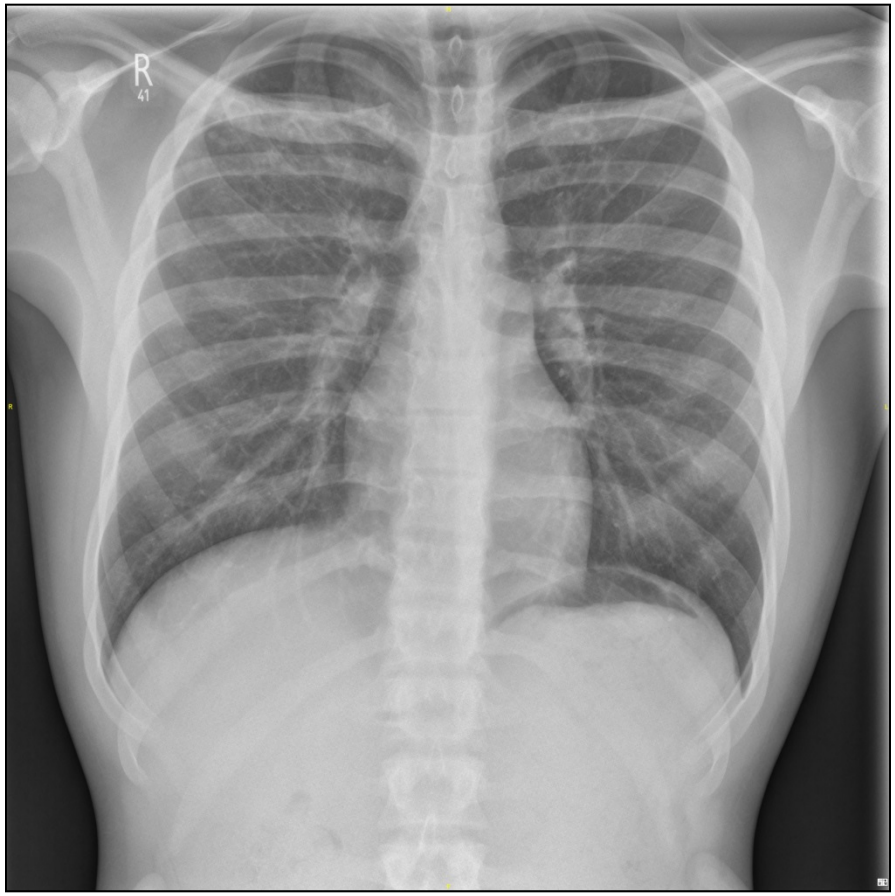
Table 6. Medicines recommended for the treatment of RR-TB and MDR-TB[a]

Group A. Fluoroquinolones[b]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
Group B. Second-line injectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[c]	(S)
Group C. Other core second-line agents[b]		Ethionamide / prothionamide	Eto / Pto
		Cycloserine / terizidone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H[h]
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	*p*-aminosalicylic acid	PAS
		Imipenem–cilastatin[d]	Ipm
		Meropenem[d]	Mpm
		Amoxicillin-clavulanate[d]	Amx-Clv
		(Thioacetazone)[e]	(T)

WHO Treatment guidelines for drug-resistant tuberculosis; 2016 update. World Health Organization 2016.

Case study

- 21 year old Somalian male, born in Denmark
- Moved to UK aged 7
- Studying medicine in Romania since 2014
- Presented December 2015
- Recent contact with TB – Israeli female student



RUL opacities/cavity
Retroperitoneal and paratracheal LN on CT

Resolved cough
10kg weight loss

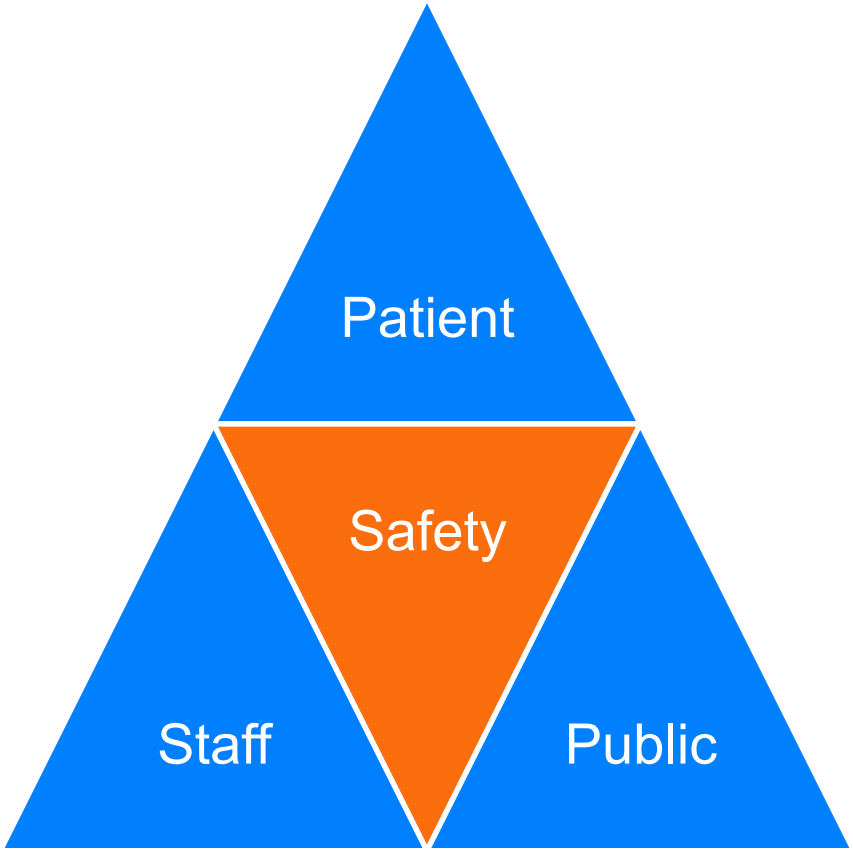
Smear negative
Rifampicin resistance probe positive in Romania

- XDR-TB confirmed on direct sputum/BAL culture

- Admitted to hospital January - June 2016
- 9-drug regime commenced

- Meropenem 1.5g BD iv
- Taught to self-administer
- Joint OPAT/ID/TB nursing care

OPAT and TB



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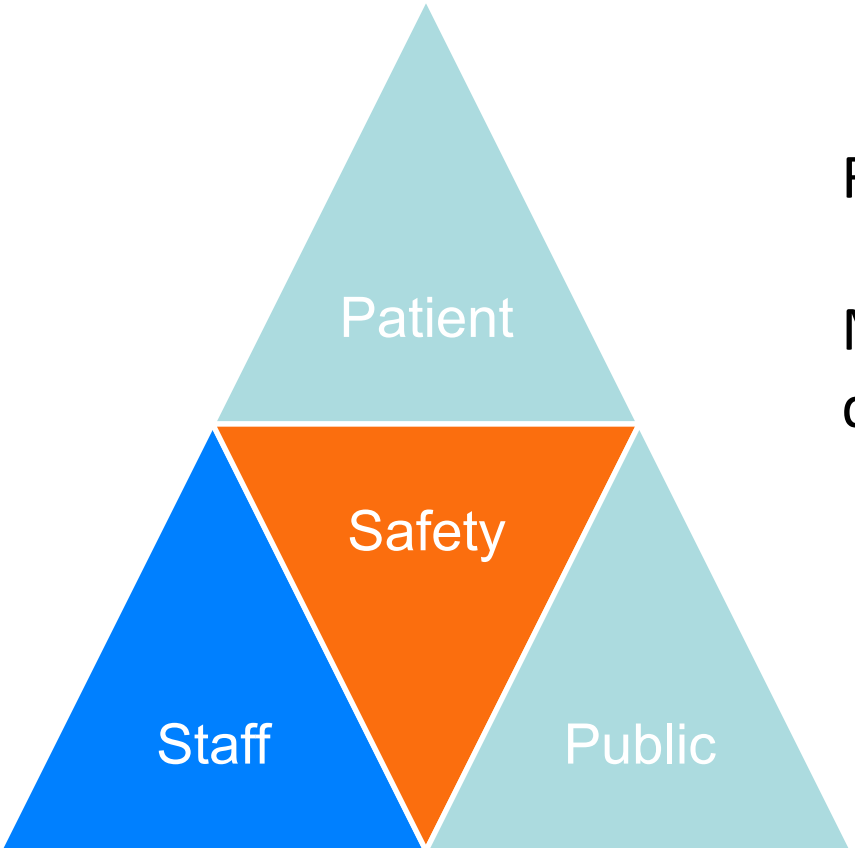
OPAT and TB

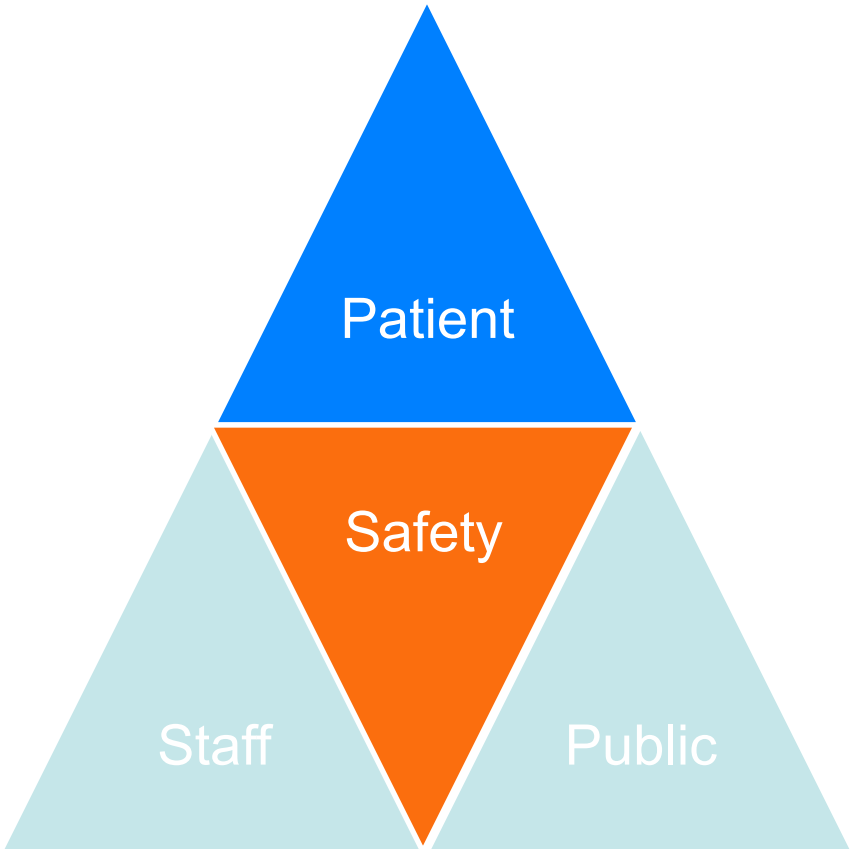


Related to infectivity

MDT decision about discharge from hospital

National Institute for Health and Care Excellence. Tuberculosis. 2016

OPAT and TB



- Line care/logistics
- Therapeutic monitoring
- Drug toxicity

Aminoglycoside monitoring

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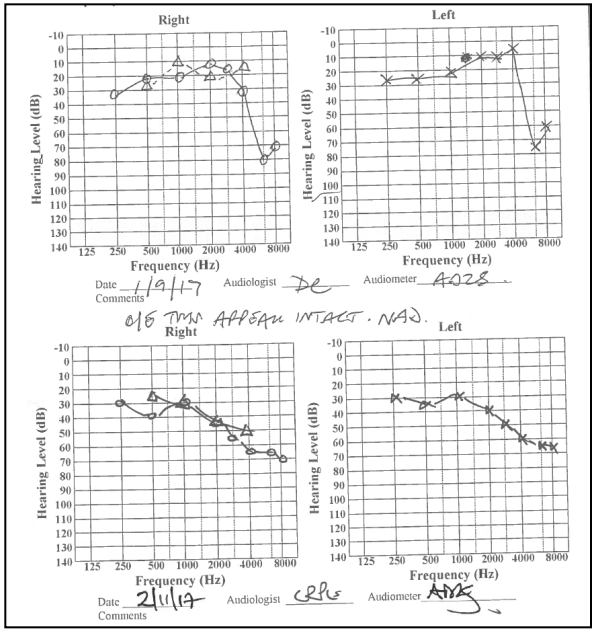
Ototoxicity

- Vestibulotoxic
- Hearing loss

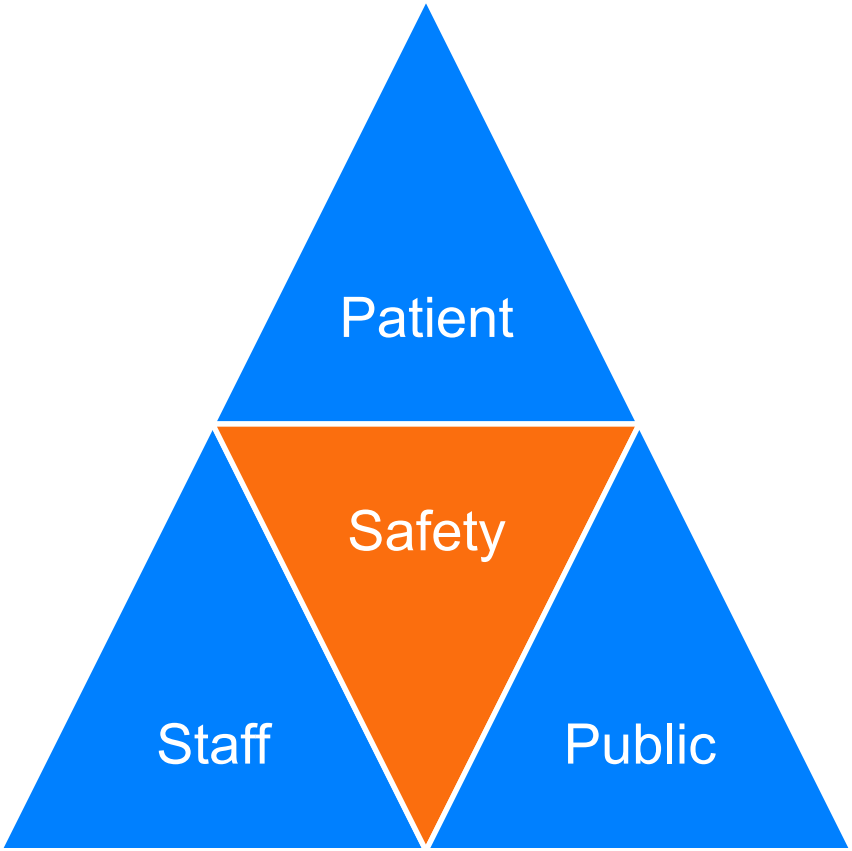


Nephrotoxicity

Monitoring required:

- Audiometry testing
- Therapeutic drug levels
- Renal function

OPAT and TB



Directly Observed Therapy (DOT)

To DOT or not to DOT?

- DOT offered for several reasons in TB care:
  - Hard to reach individuals and children
  - Substance misuse/homeless/prison
  - Concerns about adherence to therapy/poor previous adherence during treatment
  - Major cognitive or psychiatric diagnosis
  - Multi-drug resistant TB

National Institute for Health and Care Excellence. Tuberculosis. 2016

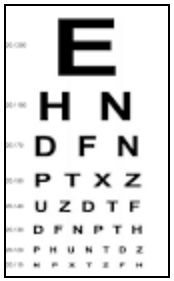
DOT

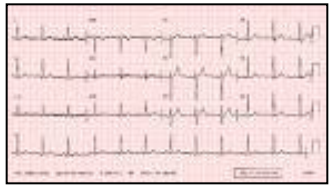
- Is iv DOT as important as DOT for the multiple oral agents?
- How to achieve for multiple dosing e.g. Meropenem tds over many months?

- Compatible with self-administration?
- Video – Observed – Therapy (VOT) potential

Case Study resumed

- Desperate to resume medical studies in Romania
- Practical issues





- Public health issues

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Contact tracing and new cases

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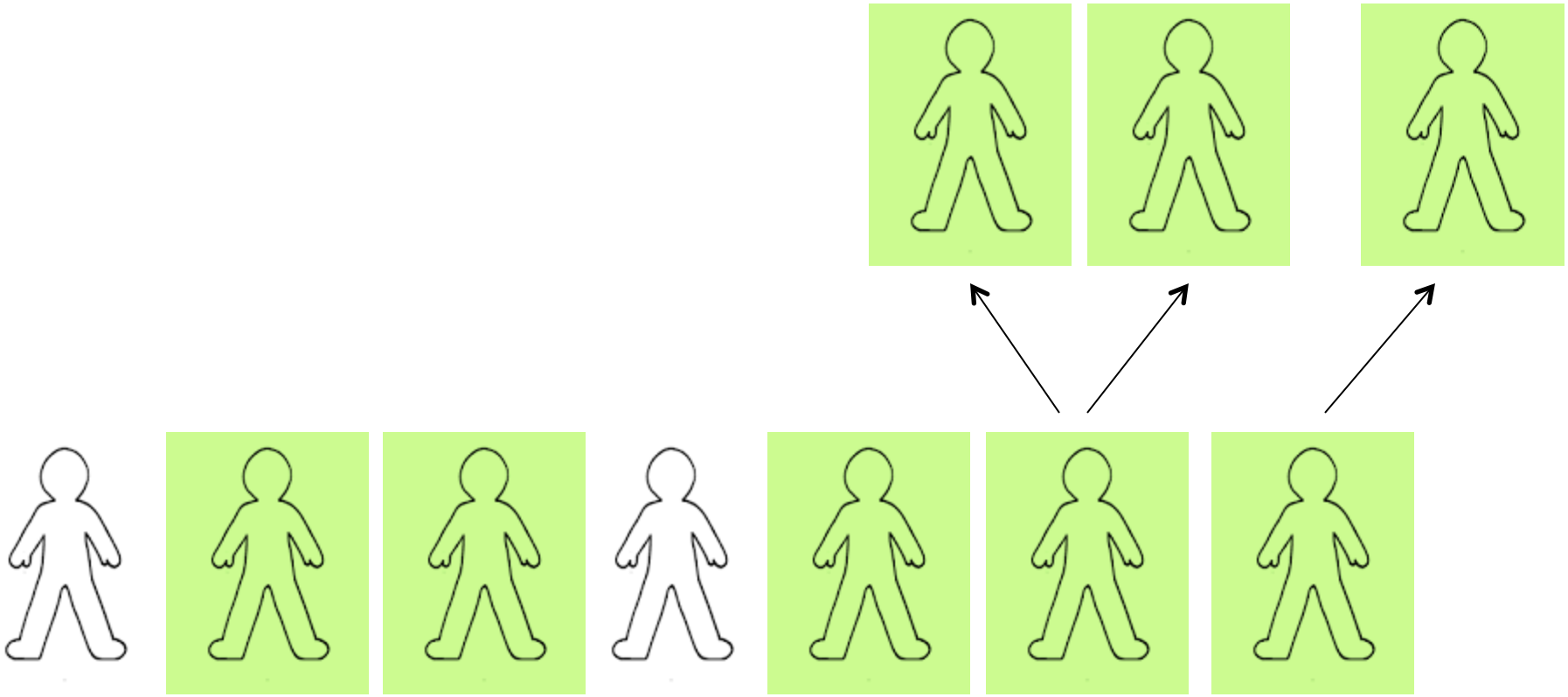

Contact tracing and new cases

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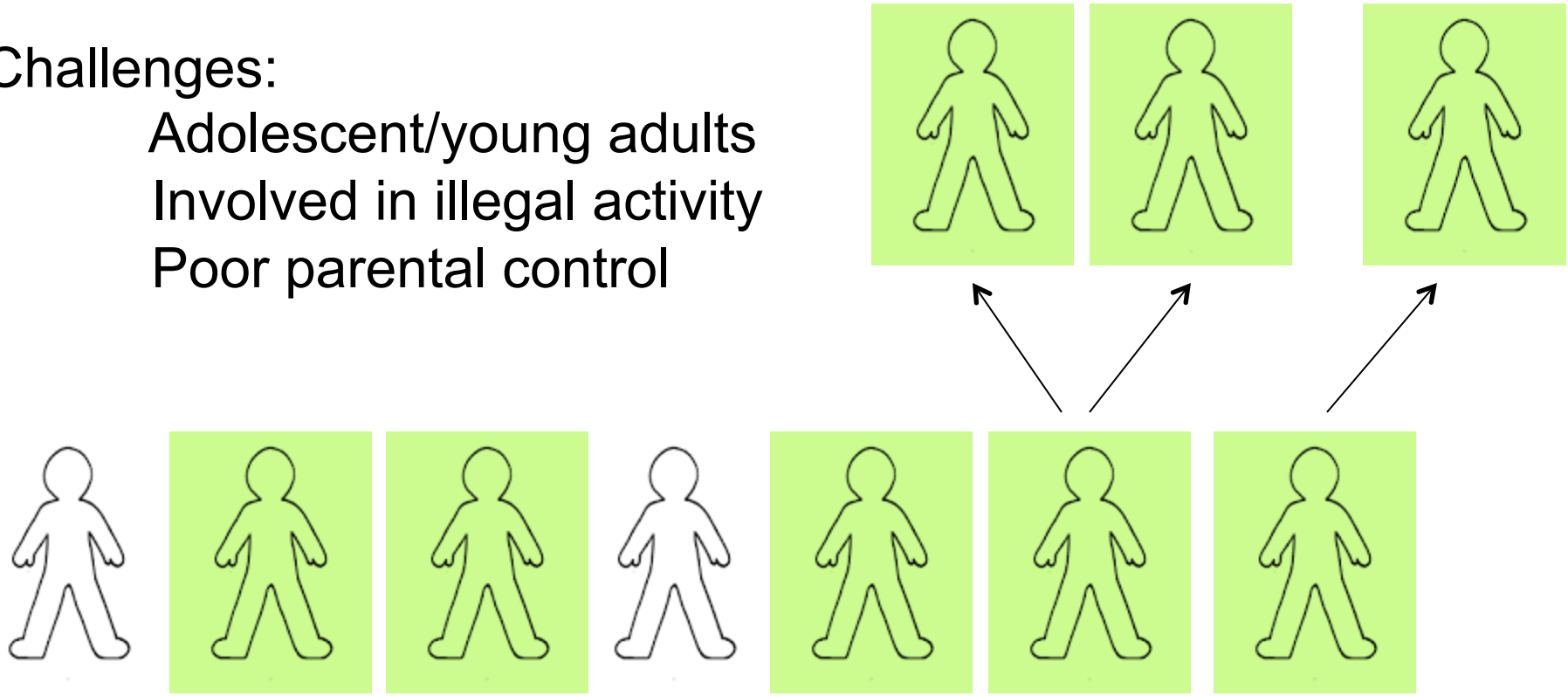
Challenges:

- Adolescent/young adults
- Involved in illegal activity
- Poor parental control



Contact tracing and new cases

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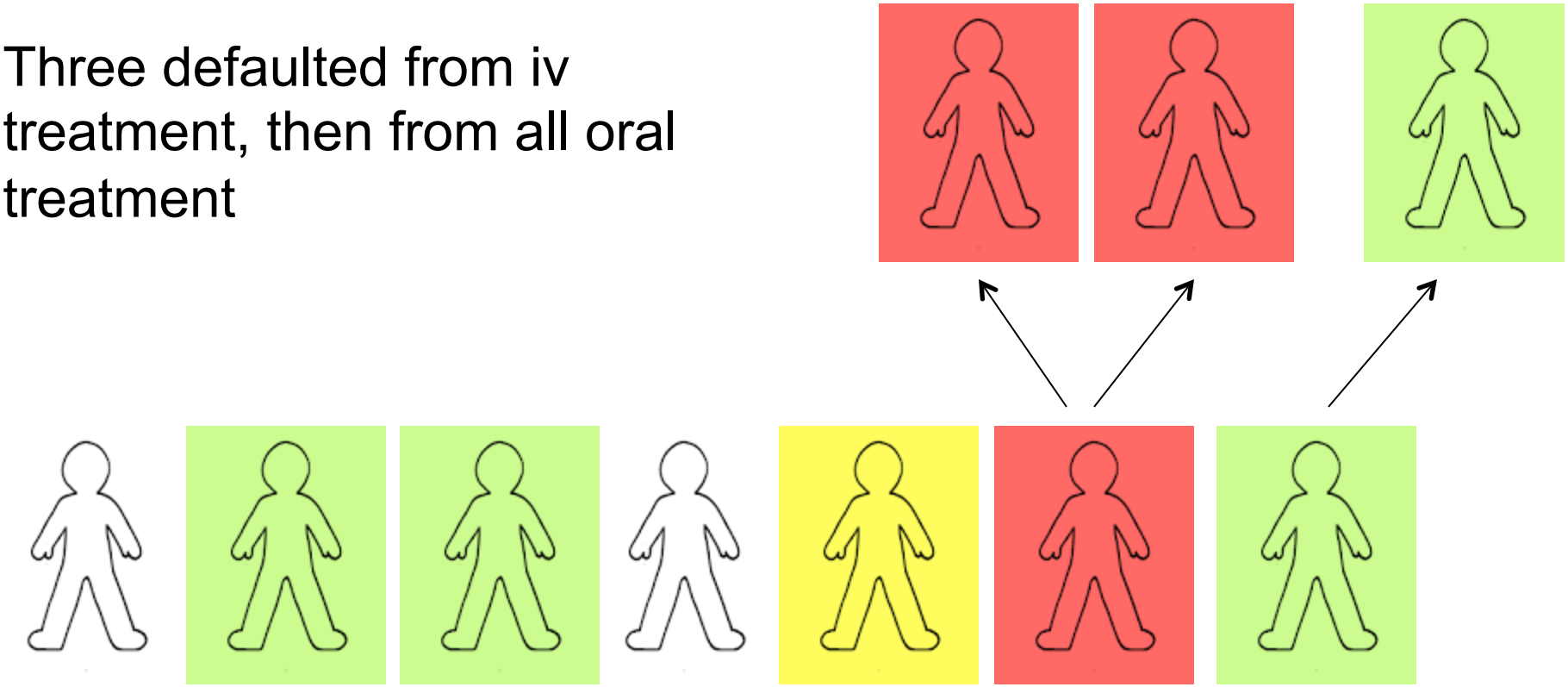
Three defaulted from iv treatment, then from all oral treatment



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Leicester TB/OPAT data

- 11 patients treated in the last 3 years

  6 XDR-TB (All on meropenem)

  5 MDR-TB (capreomycin/amikacin/meropenem)

- 920 bed days saved by 10 patients

Outcomes

- Two patients developed ototoxicity on amikacin and stopped treatment prematurely
- Three XDR-TB patients defaulted from treatment
- Two XDR-TB and three MDR-TB completed therapy

Solutions?

- Partnership with TB nursing services

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- Ideally DOT/VOT done for both oral and iv by the same team

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- Ideally DOT/VOT done for both oral and iv by the same team

- Extended nursing services needed
- May need separate commissioning

The future?

- Shorter trials of all-oral medication in progress for both MDR/XDR-TB.

Global tuberculosis report 2017. World Health Organization

Conclusions

- OPAT services invaluable in enabling discharge for patients on injectable anti-TB agents

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- OPAT services invaluable in enabling discharge for patients on injectable anti-TB agents
- However…..careful safety planning needed
- Challenging in certain groups of patients
- Self-administration/VOT versus DOT decisions need to be made individually